Migraine: pharmacotherapy in the emergency department

ABSTRACT **Migraine can be a disabling condition for the sufferer. For the small number of patients for whom home therapy fails and who seek treatment in an emergency department, several therapeutic options are available. I review the evidence regarding the effectiveness and safety of the following therapies: the phenothiazines, lignocaine (lidocaine), ketorolac, the ergot alkaloids, metoclopramide hydrochloride, the "triptans," haloperidol, pethidine (meperidine hydrochloride), and magnesium sulfate. Based on available evidence, the most effective agents seem to be prochlorperazine, chlorpromazine and sumatriptan, each of which has achieved greater than 70% efficacy in several studies.**

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Migraine headache can be a disabling condition. Patients and their general practitioners successfully manage most migraine headaches. However, a few fail to respond, and patients may present for treatment at emergency departments (EDs). Because most patients have tried oral medications before attending the ED, other routes of administration (usually parenteral) are most often used in ED. In this review, I focus on the agents that may be used to treat migraine in EDs and the evidence supporting their use.

DEFINITIONS

Most of the research in the area of migraine focuses on "common migraine" or migraine without aura. The Headache Classification Committee of the International Headache Society defines migraine without aura as an[1]

> idiopathic, recurring headache disorder manifesting in attacks lasting 4 to 72 hours. Typical characteristics are unilateral location; pulsating quality; moderate or severe intensity; aggravation by routine physical activity; and association with nausea, photophobia, and phonophobia.

The rarer migraine with aura is described as an[1]

> idiopathic, recurring headache disorder manifesting with attacks of neurological symptoms unequivocally localisable to the cerebral cortex or brain stem, usually developing gradually over 5 to 20 minutes and lasting less than 60 minutes. Headache, nausea and/or photophobia usually follow neurological aura symptoms directly or after a free interval of less than an hour. The headache usually lasts less than 72 hours, but may be completely absent.

At least 2 typical episodes are needed before this diagnosis can be assigned. In addition, there are a number of uncommon variants, such as ophthalmoplegic and abdominal migraine.

PATHOPHYSIOLOGY

The pathophysiologic features of migraine are complex, and our understanding continues to evolve. Events implicated in migraine initiation include altered electrical activity ("cortical spreading depression"[2]), a failure of brain ion homeostasis, an efflux of excitatory amino acids from nerve cells, and increased energy metabolism.[3] *N*-methyl-D-aspartate receptors are implicated in this process.[3]

The headache pain of migraine seems to result from the activation of the trigeminovascular system.[4-6] The triggers to the development of migraine headache are probably chemical and are thought to originate in the brain, blood vessel walls, and the blood. These triggers stimulate trigeminovascular axons, causing pain and the release of vasoactive neuropeptides from perivascular axons. These neuropeptides act on mast cells, endothelial cells, and platelets, resulting in increased extracellular levels of arachidonate metabolites, amines, peptides, and ions. These mediators and the resultant tissue injury lead to prolongation of pain and hyperalgesia.[6]

Serotonin has also been specifically implicated in migraine. By the activation of afferents, it causes a retrograde release of substance P. This in turn increases capillary permeability and edema.[7] In addition, magnesium has been suggested as having a role.[8]

The complexity of the mechanisms involved in the genesis of migraine makes it likely that to provide effective relief from migraine symptoms, the processes can be interrupted in several ways. Several pharmacologic agents and combinations of agents for the relief of migraine have been studied.

THERAPEUTICS

Most patients seen in EDs with severe migraine have tried to terminate their migraine headache with oral medication before going to the ED. Therefore, this review focuses on the agents that are appropriate for use in EDs. The important issues to be considered are their efficacy, the need for additional medication, and the incidence of "rebound" headache.

Problems with the evidence

An evidence-based review of the therapeutics of acute migraine is compromised by the quality of the evidence available. With the exception of the drug company–sponsored studies investigating the "triptans," most studies are small, with fewer than 50 patients in each subgroup being the norm. This means that the power of these studies to reach methodologically sound conclusions is limited. In addition, various measures of "success of treatment" are used by different study groups, which makes comparison difficult. Given these limitations, I attempt to pull together the available evidence to inform practice and form a basis for further research.

Phenothiazines: chlorpromazine and prochlorperazine

Phenothiazines are antipsychotic drugs. In the central nervous system, they are powerful antagonists of the neurotransmitter action of dopamine in the basal ganglia and limbic system. They are also potent antiemetics through effects on the chemoreceptor trigger zone, and neuroleptic actions seem to change pain perception. In addition, they are α-adrenergic antagonists (which can lead to orthostatic hypotension), chlorpromazine having greater α-blocking effect than prochlorperazine. And they have anticholinergic properties and are antagonists at both histamine and serotonin (5-hydroxytryptamine) receptors.[9]

Besides their hypotensive effect, the major side effect of phenothiazines in short-term use is dystonia. This is an idiosyncratic reaction and may occur after a single dose.[9] The mechanism by which phenothiazines act in migraine is uncertain. It is possibly the result of a combination of actions: antiserotonin effect, antidopamine effect in the chemoreceptor trigger zone, and vascular effects through their α-blocking action.[10]

The evidence about chlorpromazine

The table summarizes the success rates with the use of chlorpromazine.[11-15] Dosing regimens have varied, but a dose of 12.5 mg given intravenously (IV) and repeated at 20-minute intervals to a total dose of 37.5 mg would be representative. Intravenous fluids need to be given because of the substantial rate of orthostatic hypotension.

In comparative trials, chlorpromazine has been reported to be superior to meperidine hydrochloride (pethidine) (1 study),[16] lidocaine (lignocaine) (1 study),[14] and dihydroergotamine mesylate (DHE) (1 study)[14] and of similar effectiveness to ketorolac (1 study),[17] metoclopramide hydrochloride (1 study),[18] and sumatriptan (1 study).[15] None of the trials have reported any cases of dystonia resulting from the use of chlorpromazine in this way.

Success rates with the use of chlorpromazine to treat migraine

Study, year	Route of administration	Patients, no.	Success rate, %
Lane and Ross,[11] 1985	IV	52	94
Iserson,[12] 1983	IM	100	96
McEwen et al,[13] 1987	IM	36	47
Bell et al,[14] 1990	IV	76*	89
Kelly et al,[15] 1997	IV	42	95

IV = intravenous; IM = intramuscular
*This study had 3 arms.

The evidence about prochlorperazine

Only a few small studies have been done of the use of prochlorperazine for migraine. Success rates of 67% to 92% have been reported.[19-22] Most studies use a dose of 10 mg IV.

In comparative studies, prochlorperazine has given better pain relief than sumatriptan (1 study),[22] metoclopramide (2 studies),[20,21] and ketorolac (1 study).[23] A preliminary report of the use of rectal prochlorperazine suppositories indicated good outcomes, but its design makes evaluation difficult.[24]

Ergot alkaloids

The pharmacologic activity of ergot alkaloids derives from their ability to interact to varying degrees with subtypes of adrenergic, dopaminergic, and tryptaminergic receptors.[9] Adverse effects of the ergot alkaloids related to their pharmacologic actions include peripheral vasoconstriction, peripheral gangrene, vomiting, nausea, chest pain, pruritus, and headache.[9]

The ergot alkaloids seem to exert their antimigraine effect by strongly binding to serotonin (subtypes 1B and 1D) receptors in the blood vessels of the dura and scalp, resulting in inhibition of the trigeminal nerve–mediated neurogenic inflammation.[6,25,26]

The evidence

Studies of DHE, either alone or in combination with metoclopramide or hydroxyzine, report success rates of 23%,[14] 73%,[27] and 93%[28] when used in the dose of 1 mg IV. In comparative studies, DHE has been more effective than meperidine (1 study)[28] or lidocaine (1 study),[14] less effective than chlorpromazine (1 study),[14] and of similar effectiveness to sumatriptan (1 study)[27] and meperidine (1 study).[29] Of particular note, in the only study in which adverse events were carefully collected, 55% of patients treated with DHE had severe gastrointestinal effects.[14]

Nasal sprays of DHE are also available. Headache relief

rates of 27% at 30 minutes and 70% at 4 hours have been reported.[30] One study suggests that DHE spray is less effective than sumatriptan given subcutaneously.[31]

Haloperidol

Haloperidol is a butyrophenone, heterocyclic antipsychotic agent. It has effects on the chemoreceptor trigger zone, reducing nausea and vomiting. It is an antagonist of the central effects of dopamine and is relatively selective for the dopamine-D_2 receptor. It is also a moderate α-antagonist peripherally and has antiserotonin effects. Haloperidol is less sedating than chlorpromazine and causes less orthostatic hypotension. Dystonic reactions are haloperidol's principal side effect.[9] It is postulated that haloperidol is effective in migraine because of its antidopamine or antiserotonin effects (or both).

The evidence

No controlled or comparative trials of the use of haloperidol in migraine have been published. In a case series of 6 patients with migraine treated with 5 mg of haloperidol IV after a bolus of 500 to 1,000 mL of IV fluids, complete or substantial relief was obtained in all patients within 25 to 65 minutes. Side effects were minimal.[32]

Ketorolac

Ketorolac is a nonsteroidal anti-inflammatory agent that inhibits prostaglandin synthesis, platelet aggregation, and serotonin release from platelets.[9] It is thought that nonsteroidal anti-inflammatory drugs may act in migraine by reducing the role of prostaglandins in increasing the sensitivity of blood vessel walls to pain and in regulating smooth muscle tone and reactivity as well as decreasing changes in vascular permeability.[33]

The evidence

The doses used in studies have been 30 to 60 mg intramuscularly (IM), and a success rate of 60% has been reported.[33] In comparative studies, ketorolac (at a dose of 60 mg) has been similar in effectiveness to meperidine (2 studies)[33,34] but at a dose of 30 mg IM was less effective than meperidine (1 study).[35] Ketorolac has been reported to be less effective than prochlorperazine (1 study).[23] A small study compared the use of ketorolac, 60 mg IM, with that of chlorpromazine, 25 mg IV, and found no difference in efficacy between the agents at 2 hours.[17] However, important methodologic problems make the value of this study questionable.

Lidocaine

Lidocaine is a class 1b antiarrhythmic agent (membrane stabilizer) used for the treatment of ventricular arrhythmia. It is also a potent local anesthetic agent.[9] It was hypothesized that lidocaine might act in migraine by its membrane-stabilizing effect, which inhibits the release of vasoactive substances from platelets, thus inhibiting the sterile inflammatory response.[14]

The evidence

The usual dose used in reported studies is about 100 mg. A randomized double-blind trial comparing IV lidocaine (1 mg/kg) with placebo failed to demonstrate a difference between the 2 for the relief of the head pain of migraine.[36] In comparative studies, lidocaine has been less effective than chlorpromazine (1 study)[14] and DHE (1 study).[14] A trial of nasal lidocaine spray at a concentration of 4% reported a success rate of 55%, but the early relapse rate was 42%.[37]

Metoclopramide hydrochloride

Metoclopramide is a nonphenothiazine central dopamine antagonist and a peripheral muscarinic agonist. It increases gastric emptying and is antiemetic at the chemoreceptor trigger zone.[9] It is postulated that metoclopramide acts in patients with migraine by its antiemetic effects combined with central antidopamine effects.[38] Side effects of metoclopramide use include drowsiness and dystonia.[9]

The evidence

Uncontrolled studies of metoclopramide have reported successful relief of migraine of 75%.[39] In a placebo-controlled trial, metoclopramide in a dose of 10 mg orally was found not to be superior to placebo in the relief of headache pain from migraine.[40] However, studies of IV metoclopramide report benefit over placebo[38,41] and, in 1, a success rate of 67%.[38]

In comparative studies, metoclopramide in a dose of 10 mg IM or IV has been less effective than prochlorperazine (2 studies).[20,21] High-dose metoclopramide (0.1 mg/kg dose IV for a total of 3 doses; average dose, 16 mg) was of similar effectiveness to chlorpromazine (1 study).[18]

Meperidine

Meperidine is a synthetic narcotic analgesic that exerts its pharmacologic activity principally by binding to opioid receptors. The main adverse effects of meperidine are nausea and vomiting, respiratory depression, drowsiness, and smooth muscle spasm, particularly in the biliary tree.[9] A major concern with the use of meperidine is the possibility of the development of dependence.[9] This concern is supported by the findings of a study of 1,900 patients with chronic headache, 5% of whom were narcotic abusers.[42]

It has been hypothesized that opioids are incapable of providing lasting, effective analgesia in migraine because they depend for their effect on serotonergic projections, and patients with migraine have been shown to have central nervous system serotonin depletion.[43]

The evidence

The usual dose of meperidine is 75 mg IM or IV. A literature search covering the years 1976 through 1999 failed to identify any placebo-controlled studies of the effectiveness of meperidine for the relief of migraine headache. Clinical success rates of 22% and 50% have been reported.[16,28]

In comparative trials, meperidine, either alone or in combination with hydroxyzine and dimenhydramine, has been less effective than DHE (1 study)[28] and chlorpromazine (1 study)[16] and of similar effectiveness to DHE (1 study).[29] With respect to ketorolac, meperidine was found to give better migraine relief than ketorolac in a dose of 30 mg IM (1 study),[35] but when the ketorolac dose was 60 mg IM, the agents had similar effectiveness (2 studies).[33,34]

Sumatriptan and other "triptans"

Sumatriptan is a specific and selective serotonin$_{1D}$ agonist that has no effect on other serotonin-receptor subtypes. This receptor is found predominantly in cranial blood vessels and constricts large blood vessels that may be dilated during episodes of migraine.[44] Sumatriptan may be administered orally, subcutaneously, or by nasal spray. Adverse effects include drowsiness, weakness, dizziness, flushing, rash, pruritus, increased blood pressure, chest pain, or chest tightness. Its use is contraindicated in patients with a history of ischemic heart disease, uncontrolled hypertension, or the concomitant use of ergot preparations. A substantial number of patients have no response, for which no clinical, pharmacokinetic, or genetic explanation has been found.[45]

The antimigraine effect of sumatriptan is thought to be attributable to its effect on the serotonin$_{1D}$ receptors in cranial blood vessels.[25,44] Sumatriptan and ergot alkaloids block neurogenic inflammation by acting at prejunctional serotonin receptors on trigeminovascular fibers.[6]

The evidence

Three large double-blind studies have compared the efficacy of sumatriptan in doses of either 6 mg or 8 mg subcutaneously with placebo. Clinical success rates were 70%,[46] 75% to 80%,[47] and 70%,[48] respectively. In each study, about half the sumatriptan-treated group reported mild adverse effects, including injection site reactions, nausea, flushing, and chest heaviness. Of patients successfully treated with sumatriptan, 34% to 60% reported recurrent headache within 24 hours.[47]

In comparative studies, sumatriptan when compared with DHE IV had a significantly higher rate of relief of headache at 2 hours, but there was no difference in the rate of relief at 3 to 4 hours.[27] Sumatriptan has been more effective than DHE nasal spray.[31] It has also been of similar effectiveness to chlorpromazine (1 study)[15] and less effective than prochlorperazine (1 study).[22] Sumatriptan-treated patients had a significantly higher rate of headache recurrence within 24 hours.

Newer triptans, such as rizatriptan benzoate (10 mg orally), have had success rates of about 75% to 80%.[49]

Sumatriptan is also now available as a nasal spray (20 mg), which has a reported clinical success rate of 63% to 78%.[50,51]

Magnesium sulfate

In migraine patients, magnesium sulfate has played an important part as a regulator of neuronal excitability and, hypothetically, of headache.[52] Magnesium concentrations may also have effects on serotonin receptors, *N*-methyl-D-aspartate receptors, and nitric oxide synthesis and release.[53] Evidence suggests that about 50% of migraine sufferers have reduced concentrations of ionized magnesium.[53]

The evidence

A preliminary study reports clinical success in 35 of 40 patients after infusion of 1 g of magnesium sulfate.[8] Response was more likely in those with low ionized magnesium concentrations.

SUMMARY

Review of the evidence has some clear implications for the management of migraine in EDs. Lidocaine fails to reach acceptable efficacy standards and, as such, is not recommended for use in acute migraine. Haloperidol and magnesium sulfate need to be studied in appropriate trials before conclusions can be drawn. Ketorolac, metoclopramide, and meperidine perform a little better, but each has been shown to be inferior to other treatments. The potential for dependence and abuse must also be considered with the use of meperidine. The data on DHE are difficult to interpret because it is often used in combination with other agents, for example, metoclopramide. However, it also has been less effective than chlorpromazine and sumatriptan in the treatment of acute pain and has a high rate of adverse effects. At this time, the most effective agents seem to be prochlorperazine, chlorpromazine, and sumatriptan, each of which in a number of studies has achieved greater then 70% efficacy.

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